JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
CLINICAL TRIAL

Efficacy and safety of insulin glargine 300 U/mL vs insulin degludec in patients with type 2 diabetes: A randomized, open-label, cross-over study using continuous glucose monitoring profiles

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Keywords
Glargine 300, Hypoglycemia, Serum albumin

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J Diabetes Investig 2019; 10: 343–351

doi: 10.1111/jdi.12884

Clinical Trial Registry
University Hospital Medical Information Network Clinical Trial Registry
UMIN000031044

ABSTRACT

Aims/Introduction: Compared with glargine 100 U/mL (Gla100), glargine 300 U/mL (Gla300) and degludec (Deg) – the ultralong-acting insulins – reportedly have more stable effects and reduce the risk of hypoglycemia. Currently, they are considered to be the most useful basal insulins. The present study aimed to compare the efficacy and safety of Gla300 and Deg on glycemic control using continuous glucose monitoring.

Materials and Methods: In this single-center, open-label, parallel-group, two-period, cross-over study, 30 patients with type 2 diabetes were randomized to once-daily Gla300 followed by Deg with the same units (n = 15) or vice versa (n = 15). The primary end-points of this study were the mean percentage of time within the target glucose range of 70–180 mg/dL as efficacy and hypoglycemia of <70 mg/dL as safety indicators, as measured using continuous glucose monitoring during each treatment period.

Results: The mean percentage of time within the target glucose range was not different between Gla300 and Deg (77.8 ± 19.2 vs 76.9 ± 18.3%, P = 0.848). However, the mean percentage of time of hypoglycemia with Gla300 was significantly lower than that of Deg (1.3 ± 2.7 vs 5.5 ± 6.4%, P = 0.002). In the secondary safety end-points, the mean percentage of time of severe hypoglycemia (<54 mg/dL) or nocturnal hypoglycemia with Gla300 was also significantly lower than that of Deg.

Conclusions: The present study showed the comparable efficacy of Gla300 and Deg on glycemic control; however, the risk of hypoglycemia was markedly lower for Gla300 than for Deg.

INTRODUCTION

In patients with type 2 diabetes, intensive glucose control initiated immediately after the onset of diabetes is well known to be effective in preventing diabetic complications[1]. However, intensive glucose control reportedly increases the risk of hypoglycemia[2], and severe hypoglycemia is an important risk factor for adverse events, cardiovascular disease and mortality[3]. Furthermore, hypoglycemia and the fear of it, which are seriously concerning for patients, have been shown to inhibit aggressive treatment outcomes[4] and reduce the quality of life[5]. Therefore, achieving favorable glycemic control and preventing hypoglycemia are regarded as the most important measures in the treatment of diabetes.

Basal insulin analogs have been developed to produce a more constant and prolonged pharmacokinetic and pharmacodynamic action profile, which allows patients to optimize glycemic control while minimizing hypoglycemia risk[6,7]. While insulin glargine 100 U/mL (Gla100) is the most commonly used long-acting basal insulin, insulin glargine 300 U/mL (Gla300) and insulin degludec (Deg) are recently approved ultralong-acting, once-daily basal insulins. Both insulins have reportedly been

Received 25 March 2018; revised 6 June 2018; accepted 19 June 2018

associated with a more constant glucose-lowering effect throughout the day[8,9], reduced the risk of hypoglycemia at any time of day and reduced the risk of nocturnal hypoglycemia when compared with Gla100[8,10–12], which is presently the most widely used basal insulin. Notably, in patients with type 2 diabetes, Gla300 and Deg are individually safer than Gla100 in either basal insulin ± oral antidiabetic drugs (OADs) therapy or basal–bolus insulin therapy[13–17]. Thus, Gla100 is expected to be replaced by these two ultralong-acting insulins in the future. However, which of these two insulins is more effective and safe remains to be determined.

In the present study, patients with type 2 diabetes who were admitted and controlled for dietary intake and physical activity received Gla300 and Deg, and their efficacy and safety on glycemic control were compared.

METHODS

Study design and participants

The present single-center, randomized, open-label, parallel-group, two-period, cross-over study of patients with type 2 diabetes was carried out from July to December 2016. This study was carried out in accordance with the Declaration of Helsinki (1975, as revised in 2013). The study protocol was approved by the ethics committee of Minami Osaka Hospital (no. 2016-6), and registered with the University Hospital Medical Information Network Clinical Trial Registry (UMIN000031044) after the study was completed. All participants provided written informed consent before the study.

We enrolled 30 patients with type 2 diabetes, including 18 men and 12 women, who were admitted to Minami Osaka Hospital, Osaka, Japan, for the purpose of glycemic control and education. Inclusion criteria comprised of age ≥20 years, diagnosed with type 2 diabetes based on the American Diabetes Association Criteria[18] for at least 1 year before screening, having OADs and/or any insulin therapy for at least 6 months before screening. Patients with a glycated hemoglobin (HbA1c) level of <6.5% (48 mmol/mol) or >11.0% (97 mmol/mol) at screening, unstable retinopathy, diabetic kidney disease with severely decreased estimated glomerular filtration rate (<30 mL/min/1.73 m^2) or overt proteinuria, pregnant women, history of gastrointestinal surgery, presence of cancer and clinically important cardiac, renal, hepatic or other systemic diseases were excluded from this study.

Figure 1 shows the study protocol. Participants enrolled in the study were randomized to Gla300-Deg (Gla300/Deg) or Deg-Gla300 (Deg/Gla300) sequence groups. All participants received once-daily injections of either Gla300 (Sanofi, Paris, France) or Deg (Novo Nordisk, Bagsværd, Denmark), and each basal insulin was administered in accordance with the previous report[9], with a small modification in the first treatment period (Figure 1; treatment period 1). In brief, participants previously treated with OADs continued their prestudy OAD treatment without any change in dose or regimen. The starting dose of Gla300 or Deg for basal insulin-naïve participants was 4 U. Participants receiving basal insulin before the study were switched to Gla300 or Deg on a unit-for-unit dose basis without any change of bolus insulin. Participants receiving premixed insulin before the study were switched to basal–bolus insulin therapy with Gla300 or Deg, and the short-acting insulin with the same dose of intermediate-acting and short-acting insulin included in the premixed insulin, respectively. Then, based on the self-monitoring of blood glucose (SMBG), basal insulin doses were titrated to a target preprandial glucose concentration of 100–130 mg/dL at breakfast. We have >10 days titration period after randomization to eliminate the effect of the release of glucose toxicity. The basal insulin dose was titrated no more often than every 3–4 days. Furthermore, bolus insulin doses were titrated to the target preprandial and before bed glucose concentrations of 100–130 mg/dL. After setting the insulin doses, we confirmed that fluctuations in glucose levels before breakfast, lunch, supper and bedtime were individually stabilized within 10% for ≥3 days, and hypoglycemia was not documented by SMBG. After that, we evaluated their glycemic control in a blinded fashion using iPro™2 Professional continuous glucose monitoring (CGM, Medtronic, Inc.; Northridge, California, USA) for five consecutive days. Subsequently, their basal insulin was switched from Gla300 to Deg and vice versa in the second treatment period (Figure 1). After washing out the former basal insulin for more than 3–4 days, confirmed by SMBG profile, we again evaluated their glycemic control using CGM for five consecutive days. Dosage of OADs, bolus insulin and basal insulin was not changed in the second treatment period. CGM recorded glucose values for the last 5 days in each treatment period, and we used 3 days in the middle to complete the 24-h recording sets.

Each participant was given the following hospital diet with the same calorie and carbohydrate amount: 25–30 kcal/ideal bodyweight/day with a certain component ratio of calories (carbohydrate 60%, proteins 17% and lipids 23%; breakfast 30%, lunch 35% and supper 35%). To match the physical activity during the study period, patients were prohibited from carrying out excessive exercise, except moderate aerobic exercise for 30 min per day.

Outcome measures

The primary end-points of the present study included the efficacy and safety outcomes based on the CGM parameters. The efficacy outcome was the mean percentage of time within the predefined CGM glucose range of 70–180 mg/dL, expressed as target range, for three consecutive days of each treatment period. The safety outcome was the mean percentage of time with glucose levels of <70 mg/dL, expressed as hypoglycemic range[19,20]. Secondary end-points based on CGM included the 24-h mean glucose level, nocturnal (00.00–06.00 hours), morning (08.00–12.00 hours) and afternoon (12.00–24.00 hours) mean glucose levels; 24-h standard deviation (SD) of the glucose levels; 24-h coefficients of variation (CV) of the glucose levels[21]; 24-h M-value (target glucose level 100 mg/dL)[22]; and

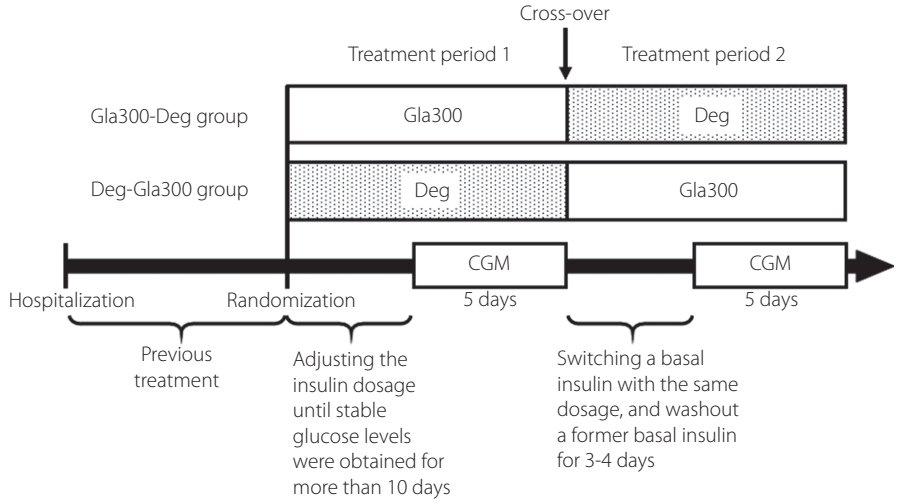

Figure 1 | The study protocol. CGM, continuous glucose monitoring; Deg, insulin degludec; Gla300, insulin glargine 300 U/mL.

mean percentage of time with severe hypoglycemia (<54 mg/dL)[23], with nocturnal (00.00–06.00 hours) hypoglycemia (<70 mg/dL) and with hyperglycemia (≥180 mg/dL) for three consecutive days. The mean amplitude of glycemic excursion[22,24] was calculated from the CGM data considering the glycemic peaks and nadirs recorded over a 24-h period for three consecutive days. The mean of daily difference (MODD) for a 24-h period was used as an index of day-to-day glucose variability[22,24].

Statistical analysis

Data are expressed as the mean ± SD, unless otherwise indicated. Findings were compared between two treatments using the Student's *t*-test[25]. The number of hypoglycemic events on each clock time was compared using the McNemar's test. The carry over and period effects in the cross-over study were verified using the repeated measured analysis of variance (ANOVA) according to the Grieve method[26]. A *P*-value of <0.05 was considered significant for all other analyses. Statistical analyses were carried it using JMP 10 software (SAS Institute Inc., Cary, North Carolina, USA).

RESULTS

Participant characteristics

A total of 30 participants with type 2 diabetes enrolled in the study were randomized for Gla300/Deg (n = 15) or Deg/Gla300 (n = 15) and were included in the intention-to-treat population. All participants completed the study (Figure S1). Initially, the breakdown of treatment was insulin naïve and OADs (n = 13), basal–bolus insulin therapy (n = 5), basal insulin ± OADs therapy (n = 4) and premixed insulin therapy (n = 8). Gla100 had been used as a basal insulin by all patients. Baseline characteristics were similar in all treatment groups (Table 1). After the entry, patients received either basal–bolus insulin therapy (n = 13) or basal insulin ± OADs therapy (n = 17). The basal insulin doses titrated during treatment period 1 (Figure 1) were insignificantly different between the Gla300/Deg and Deg/Gla300 groups (0.17 ± 0.10 and 0.22 ± 0.15 U/kg/day, respectively).

Comparison of efficacy and safety between Gla300 and Deg

The primary end-points of the present study were the mean percentage of time within the target glucose range of 70–180 mg/dL as efficacy and with hypoglycemia (<70 mg/dL) as safety. The mean percentage of time within the target glucose range was not different between Gla300 and Deg. However, the mean percentage of time with hypoglycemia with Deg was much higher than that of Gla300 (Table 2). Regarding the mean percentage of time within the target glucose range and time with hypoglycemia, neither the carry over (P = 0.0636 and 0.4141, respectively) nor the period effect (P = 0.2712 and 0.1257, respectively) was observed in the present cross-over study.

For the secondary efficacy end-points, the 24-h mean glucose level; the nocturnal (00.00–06.00 hours), morning (08.00–12.00 hours) and afternoon (12.00–24.00 hours) mean glucose levels or the mean percentage of time with hyperglycemia (≥180 mg/dL) were insignificantly different between the two insulins. No significant differences were observed between the two insulins in any of the indices of diurnal variation in glucose levels; that is, the 24-h SD of the glucose levels, the 24-h M-value and mean amplitude of glycemic excursion. However, CV, an index of a more sensitive index of diurnal variation in glucose level and MODD, and an index of day-to-day variation, were significantly higher for Deg than for Gla300 (Table 2). Regarding the secondary safety end-points, the mean percentage of time with severe hypoglycemia (<54 mg/dL) and nocturnal hypoglycemia were also evaluated. Both values were markedly

Table 1 | Baseline characteristics of randomized participants

	Overall (n = 30)	Gla300/Deg (n = 15)	Deg/Gla300 (n = 15)	P-value*
Age (years)	69.5 ± 11.3	71.1 ± 9.2	67.9 ± 13.2	0.449
Duration of diabetes (years)	18.3 ± 11.3	18.5 ± 10.4	18.1 ± 12.5	0.937
Male, n (%)	18 (60.0)	8 (53.3)	10 (66.7)	0.151
BMI (kg/m^2)	24.6 ± 4.8	25.3 ± 4.8	24.0 ± 5.0	0.468
HbA1c (%)	8.2 ± 1.9	8.5 ± 2.2	8.0 ± 1.5	0.469
S-CPR (ng/mL)	1.8 ± 1.7	1.9 ± 1.8	1.8 ± 1.6	0.883
eGFR (mL/min/1.73 m^2)	67.9 ± 22.7	66.6 ± 25.0	69.1 ± 20.8	0.763
S-albumin (g/dL)	3.7 ± 0.5	3.8 ± 0.5	3.7 ± 0.5	0.589
Prestudy treatment				
OADs only (n)	13	6	7	0.337
Basal/bolus insulin (n)	5	3	2	0.374
Basal insulin dosage (U/day)	13.6 ± 15.1	6.0 ± 3.5	25.0 ± 21.2	0.196
Bolus insulin dosage (U/day)	16.8 ± 9.1	12.0 ± 4.0	24.0 ± 11.3	0.170
Basal insulin ± OADs (n)	4	2	2	1.000
Basal insulin dosage (U/day)	15.5 ± 10.0	22.0 ± 11.3	9.0 ± 1.4	0.248
Premixed insulin (n)	8	4	4	1.000
Dosage (U/day)	21.3 ± 9.2	21.0 ± 9.6	21.5 ± 10.2	0.946
Antidiabetic agents other than insulin				
DPP4 inhibitor (n)	14	7	7	1.000
Metformin (n)	10	3	7	0.123
SGLT2 inhibitor (n)	2	2	0	0.153
Sulfonylurea (n)	3	2	1	0.559
Glinide (n)	1	1	0	0.326
α-GI (n)	3	1	2	0.559
GLP-1RA (n)	1	1	0	0.326

Values are expressed as mean ± standard deviation. *Data were compared between two sequence groups using the Student's t-test or χ^2-test. Antidiabetic drugs other than insulin were not changed throughout the study period. α-GI, alpha-glucosidase inhibitor; BMI, body mass index; DPP4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonists; HbA1c, glycated hemoglobin; OADs, oral antidiabetic drugs; S-CPR, serum C-peptide immunoreactivity; s-albumin, serum albumin; SGLT2, sodium–glucose cotransporter 2.

higher for patients treated with Deg than those treated with Gla300 (Table 2). Figure 2 shows the average daily glucose profiles for three consecutive days measured using CGM. The glucose variations were similar between all participants (Figure 2a) and those treated with basal insulin ± OADs therapy (Figure 2b). Although the nocturnal (00.00–06.00 hours) mean glucose levels were insignificantly different between Gla300 and Deg (Table 2), those for Deg tended to be lower than those for Gla300 (Figure 2). Therefore, more patients were developing substantial hypoglycemia at night during Deg treatment than during Gla300 treatment (Figure S2). This trend was equally observed in both, all patients and those only receiving basal insulin ± OADs therapy. Although no significant difference between Gla300 and Deg was observed in preprandial glucose levels either (Table 2), they tended to be lower for Deg than for Gla300 (Figure 2).

Correlation between hypoglycemia and serum albumin concentration in patients treated with Deg

In the present study, factors associated with hypoglycemia were also investigated. Although no association between hypoglycemia and serum albumin concentrations was observed during Gla300 treatment (Figure 3a,c), serum albumin concentrations were strongly, negatively correlated with both the mean percentage of time with daily hypoglycemia and with nocturnal hypoglycemia (Figure 3b,d). Furthermore, because the correlations with daily and nocturnal hypoglycemia were almost comparable (Figure 3b,d), the association between hypoalbuminemia and hypoglycemia appeared to mainly reflect the association with nocturnal hypoglycemia. Age, sex, duration of diabetes, bodyweight, body mass index, C-peptide reactivity, estimated glomerular filtration rate, HbA1c, low-density lipoprotein, high-density lipoprotein or triglyceride were not associated with hypoglycemia (data not shown).

DISCUSSION

In the present study using CGM, the efficacy and safety were compared between Gla300 and Deg on glycemic control in patients with type 2 diabetes. When Gla300 and Deg were compared at the same units, they achieved comparable glycemic control and efficacy. However, regarding the safety, the risk of hypoglycemia was markedly lower for Gla300 than for Deg.

Because severe hypoglycemia and nocturnal hypoglycemia have been recognized as major limiting factors for intensive

Table 2 | Continuous glucose monitoring parameters of glucose variability in patients with insulin glargine 300 U/mL or degludec

	Gla300	Deg	*P*-value
Mean percentage of time with target glucose range 70–180 mg/dL (%)	77.8 ± 19.2	76.9 ± 18.3	0.848
Mean percentage of time with hyperglycemia ≥180 mg/dL (%)	20.9 ± 19.0	17.7 ± 18.3	0.505
24-h SD (mg/dL)	36.3 ± 11.7	38.9 ± 11.7	0.094
24-h M-value (target glucose level 100 mg/dL)	10.1 ± 9.0	10.0 ± 9.1	0.938
24 h CV (%)	25.0 ± 6.3	28.9 ± 7.1	0.028*
00.00–06.00 hours CV (%)	13.9 ± 6.5	18.5 ± 9.5	0.031*
MAGE (mg/dL)	91.5 ± 27.2	92.4 ± 24.6	0.885
MODD (mg/dL)	22.5 ± 8.7	27.6 ± 9.8	0.035*
24-h mean glucose level (mg/dL)	144.4 ± 36.3	134.3 ± 26.5	0.141
00.00–06.00 hours mean glucose level (mg/dL)	113.9 ± 28.3	101.8 ± 34.4	0.107
08.00–12.00 hours mean glucose level (mg/dL)	166.8 ± 38.7	154.7 ± 41.1	0.199
12.00–24.00 hours mean glucose level (mg/dL)	156.2 ± 33.3	148.1 ± 32.9	0.317
Preprandial glucose level at breakfast (mg/dL)	122.2 ± 22.2	111.1 ± 30.5	0.100
Preprandial glucose level at lunch (mg/dL)	141.3 ± 28.1	129.5 ± 25.5	0.094
Preprandial glucose level at supper (mg/dL)	136.7 ± 28.3	126.1 ± 34.1	0.193
Mean percentage of time with hypoglycemia <70 mg/dL (%)	1.3 ± 2.7	5.5 ± 6.4	0.002*
Mean percentage of time with severe hypoglycemia <54 mg/dL (%)	0.04 ± 0.18	1.8 ± 3.0	0.003*
Mean percentage of time with nocturnal hypoglycemia <70 mg/dL (%)	1.1 ± 2.4	4.2 ± 5.8	0.009*

Values are expressed as mean ± standard deviation. *Data were compared using Student's *t*-test. A *P*-value of <0.05 was considered significant. CV, coefficient of variation; MAGE, the mean amplitude of glycemic excursion; MODD, mean of daily difference; SD, standard deviation of the glucose levels.

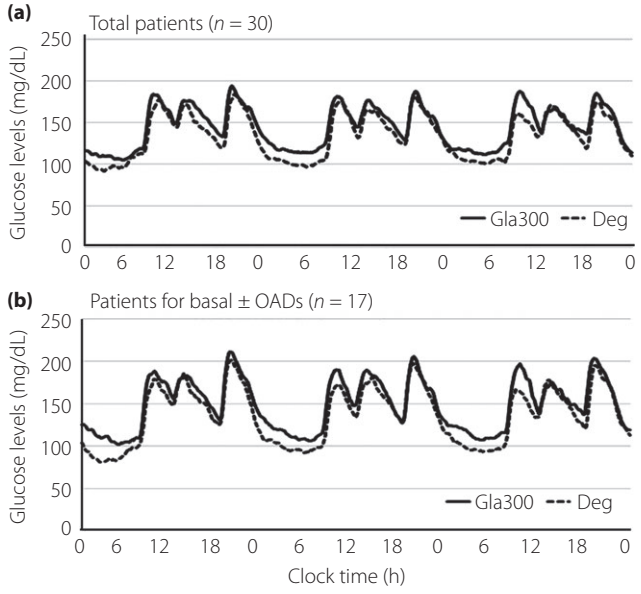

Figure 2 | The 24-h glucose variations based on continuous glucose monitoring. The mean glucose variations for 3 days of (a) the total patients (n = 30) and (b) patients treated with basal insulin ± oral antidiabetic drugs (OADs) therapy (n = 17). Solid and dotted lines show the glucose variations in patients receiving insulin glargine 300 U/mL (Gla300) and degludec (Deg), respectively.

glycemic control[27], and risk factors for adverse events, cardiovascular disease and mortality[3,28], important measures for the treatment of diabetes have been developed mainly to prevent hypoglycemia and to simultaneously achieve favorable glycemic control. The present study showed that the frequency of hypoglycemia (particularly nocturnal hypoglycemia) recorded by CGM was significantly lower during Gla300 treatment than during Deg treatment. Furthermore, in the present study, although no significant differences in the indices of diurnal variation (the 24-h SD of the glucose levels, the 24-h M-value and mean amplitude of glycemic excursion) were observed between Deg and Gla300 treatments, CV, an index of a more sensitive index of diurnal variation in glucose level and MODD, and an index of day-to-day variation were significantly higher during Deg treatment than during Gla300 treatment. As a cause, there was a significant difference in the frequency of nocturnal hypoglycemia even though there was no difference in the mean glucose level, and it was considered that there was a significant difference in CV between the two groups. Because the fasting plasma glucose (FPG) levels in patients who developed nocturnal hypoglycemia were significantly higher in the morning after the event than on the previous day (data not shown), the significantly higher MODD during Deg treatment was assumed to have been attributable to the Somogyi effect induced by nocturnal hypoglycemia. Either finding indicates the superiority of Gla300 to Deg in safety. Comparing Gla300 and Deg 24-h pharmacodynamics and pharmacokinetics, there are reports of Gla300 providing less fluctuating steady-state pharmacodynamics profiles (i.e., lower within-day variability) and more evenly distributed pharmacokinetic profiles, compared with Deg. It was thought that this action profile was linked to the results of the present study this time[29].

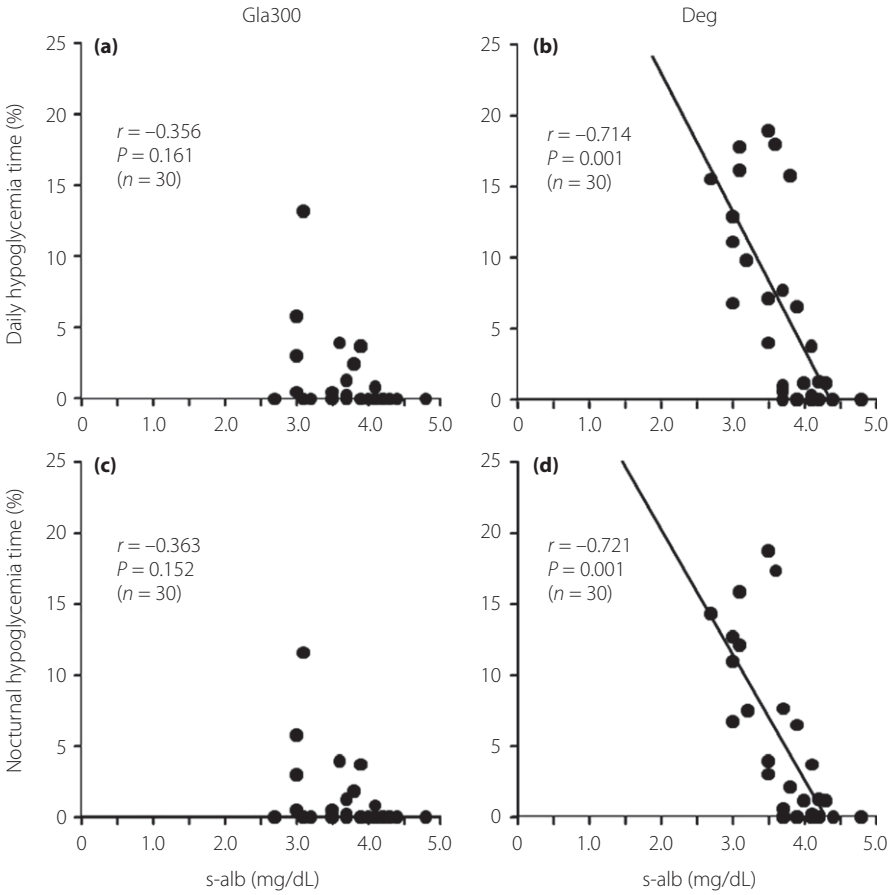

Figure 3 | The relationship between hypoglycemia and serum albumin (s-alb) concentration. The association between the mean percentage of time and (a, b) daily hypoglycemia (<70 mg/dL) or (c, d) nocturnal (00.00–06.00 hours) hypoglycemia for three consecutive days based on continuous glucose monitoring and serum albumin concentrations are shown. Daily or nocturnal hypoglycemia time was strongly correlated with serum albumin concentrations in (b, d) patients treated with insulin degludec (Deg), unlike (a, c) with insulin glargine 300 U/mL (Gla300) treatment. The Pearson product-moment correlation coefficient (*r*) was used to study the relationship. A *P*-value of <0.05 was considered significant.

In the present study, the basal insulin doses were titrated to the mild target FPG range of 100–130 mg/dL to prevent hypoglycemia, and the target was achieved (Table 2). It should be noted that even after adjusting the basal insulin doses to the target glucose levels, which seemed relatively safe, nocturnal hypoglycemia was caused by Deg in a very large number of patients (Figure 2S). Many studies showed that hypoglycemic events were markedly less frequently caused by Deg than by Gla100[30], and the incidence of hypoglycemic events in patients receiving Deg in these studies was much lower than that in the present study[14,16,17,31]. The discrepancy in the incidence of hypoglycemia between the previous and present studies might be attributable to different methods in monitoring glucose levels and definitions of hypoglycemia. In the SWITCH 1 and 2 trials[16,31] and the BEGIN study[14,17], the basal insulin doses were adjusted to a target FPG range of 70–90 mg/dL, and achieved FPG levels that were consistent with the levels obtained in the present study (100–130 mg/dL). However, because glucose levels were monitored with SMBG instead of CGM, all asymptomatic nocturnal hypoglycemic events were not always detected[32]. Furthermore, because hypoglycemia was defined as a plasma glucose level of <56 mg/dL in these studies, some hypoglycemic events (plasma glucose of 56–70 mg/dL) were not counted. Thus, many hypoglycemic events, particularly nocturnal hypoglycemia, should be considered in these studies. In fact, another study in which FPG levels were controlled at levels comparable with those observed in the present study reported that hypoglycemia (plasma glucose of <70 mg/dL) and nocturnal hypoglycemia monitored with CGM were frequently observed in patients receiving Deg[20], which is consistent with the present study. Thus, when Deg is used, nocturnal hypoglycemia should be carefully considered. In addition, because the insulin requirement is reported to be lower for Deg than for Gla100 to achieve comparable glycemic control[30], insulin doses can be reduced at the time of switching from Gla300 to Deg.

More interestingly, the present study showed that the mean percentage of time with hypoglycemia, particularly with nocturnal hypoglycemia, during Deg treatment significantly, negatively correlated with albumin levels (Figure 3). Although the reasons for the association between decreased albumin levels and hypoglycemia caused by Deg are unknown, a possible reason was identified. It is the reversible binding of Deg to albumin. Deg forms a depot of soluble multihexamers after injection into the subcutaneous tissue, with subsequent stable and slow release of monomers into the circulation[33]. Although this is the major mechanism underlying the prolonged and stable effect of Deg, the binding of Deg to albumin is also one of the factors explaining the stability and prolonged duration of Deg effects[33]. Gla300 does not bind to albumin[34,35]. In contrast, ≥99% of Deg reversibly binds to albumin and is released from albumin in the target tissue to exert the glucose-lowering effects[36,37]. As the serum albumin levels are much higher than Deg concentrations at therapeutic doses (>10,000-fold), the pharmacokinetic properties of Deg are not considered to be affected by even large changes in albumin concentrations[36]. Deg has determined the association constant ($Ka = B/[F \times HSAimm]$), B/F is the ratio between bound and free insulin, and HSAimm is the total concentration of immobilized albumin[33]. Furthermore, serum albumin levels become high values in the daytime, and the lowest values at night[38]. It means when serum albumin levels decrease at night, bound insulin decreases; in contrast, free insulin increases to maintain a constant Ka. As free insulin exerts the effect attached to the insulin receptor, Deg might exert a strong effect at night and cause nocturnal hypoglycemia. However, a study that actually examines the association between the efficacy or safety of Deg and albumin concentrations has not been published yet. Furthermore, competitive substances, such as bilirubin and free fatty acids (FFA), are known to actually affect the affinity between drugs and albumin[39]. Increased FFA levels at night were associated with increased growth hormone levels[40]. Notably, in patients with diabetes, the inhibitory effect of insulin on FFA is reduced[41], and FFA levels markedly increase at night[42]. Because insulin detemir, known to bind to albumin as with Deg, has been shown to be released from albumin in association with an increased ratio of FFA to albumin levels[43], the reported FFA concentrations at night in patients with diabetes[42] can theoretically induce insulin release at low albumin concentrations[43]. Thus, the combination of hypoalbuminemia and increased FFA levels at night might lead to nocturnal hypoglycemia during Deg treatment.

The present study had several limitations. The first limitation was that we did not assess the possibility that the doses required to yield the same effect might differ between Gla300 and Deg. In the present short-term study, insulin doses titrated during the first treatment period were not changed during the study period, and Gla300 and Deg were also administered at the same units after switching. This study revealed the differences between Gla300 and Deg effects with the same units on glycemic variability. However, according to studies comparing Deg and Gla100 for the efficacy and safety on long-term glycemic control, the insulin requirement to achieve the same level of glycemic control with Deg is lower than that with Gla100, and these studies showed that the incidence of hypoglycemia caused by Deg is markedly lower with reduced insulin doses[16,30,31]. If the basal insulin doses had been titrated based on the incidence of hypoglycemia and FPG levels after switching between Gla300 and Deg, the administered amount of insulin would have been smaller during Deg treatment than during Gla300 treatment; consequently, the incidence of hypoglycemia might have been reduced. To compare the efficacy and safety in actual treatment, long-term glycemic control, incidence of hypoglycemia, and risks of cardiovascular events and death should be investigated in a multicenter, randomized, double-blinded, parallel-group study with a protocol requiring adjustment of insulin doses based on the glycemic status of daily life.

The second limitation was that although Deg more likely causes nocturnal hypoglycemia in patients with hypoalbuminemia (Figure 3), the correlation between nocturnal hypoglycemia and diurnal variation of serum albumin was not investigated in the present study. To ensure the efficacy and safety of Deg, further studies should be carried out on whether or how hypoalbuminemia affects glycemic control with Deg. If hypoalbuminemia is a predictor of nocturnal hypoglycemia caused by Deg, it might be one of the indicators in selecting appropriate treatment.

The efficacy and safety of Gla300 and Deg in patients with type 2 diabetes were compared and analyzed in a randomized cross-over study using CGM. When comparing these two insulins with the same units, their effects were similar in achieving the target glycemic control; however, Gla300 was safer than Deg with regard to hypoglycemia, particularly nocturnal hypoglycemia. Furthermore, the present study suggested that hypoalbuminemia might be a predictor of nocturnal hypoglycemia caused by Deg.

The third limitation was FFA and Deg unbound albumin were not measured in the present study, so the involvement of FFA and Deg unbound albumin remains unknown. Therefore, it needs to be investigated in future studies.

ACKNOWLEDGMENTS

The authors were fully responsible for all content and editorial decisions, were involved in all stages of manuscript development, and have approved the final version. The authors thank the staff of Minami Osaka Hospital for their great help.

DISCLOSURE

YK has received honoraria for lectures or speaker's fee from Sanofi K.K., Novo Nordisk Pharma, MSD, Takeda Pharmaceutical Co., Sanofi-Aventis, Ono Pharmaceutical Co., Boehringer Ingelheim, Taisho Toyama Pharmaceutical Co. and Novartis Pharma K.K. The other authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1| Enrollment of participants in the study.
Figure S2| Participants with documented hypoglycemic events.